REMARKS/ARGUMENTS

Claims 124-127 and 129-133 remain pending in this application. Claim 127 has been canceled without prejudice or disclaimer. Claims 132 and 133 have been amended to remove reference to the term "native sequence", whereas Claims 124, 132 and 133 have been amended to remove references to the term "extracellular domain". Applicants believe that these amendments make the claims more closely represent what Applicants have always considered their invention. Claims 124-126 and 129-133 are now under consideration.

In this submission, Applicants further present additional references in support of Applicants' arguments presented in their response of January 9, 2006, which is incorporated herewith in its entirety. Applicants note that some of the references listed in the enclosed Information Disclosure Statement are provided in the form of full-text articles, while others are provided as abstracts. Applicants submit that the full-text articles are provided solely because they are available, and that Applicants do not intend to make any distinction among the references, or to indicate that some references in the IDS are more pertinent or material than others.

Applicants respectfully traverse the present rejections.

Priority

First of all, Applicants respectfully maintain the position that the instant specification discloses at least one credible, substantial and specific asserted utility for the PRO1111 polypeptides, for the reasons discussed previously in Applicants' Responses. Applicants maintain that the results of the 'gene amplification' assay (Example 170) provides patentable utility for PRO1111. This utility was first disclosed in the U.S. Provisional Patent Application Serial No. 60/141,037, filed June 23, 1999, priority for which has been claimed in this application. Applicants also maintain that they are entitled to an effective filing date of at least **June 23, 1999** based on the 'gene amplification' assay results for PRO1111 disclosed in the earlier application.

Arguments

The Examiner has indicated that the results of the gene amplification assay was not found to be persuasive for utility for PRO1111 polypeptides.

Applicants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1111 polypeptide of SEQ ID NO:229 and that the increase in gene amplification for the DNA encoding PRO1111 is sufficient to confer patentable utility to the instantly claimed PRO1111 polypeptides.

As discussed previously, it is not a legal requirement to establish a "necessary" correlation between an increase in gene copy number and protein expression levels or to find evidence that protein levels can be accurately predicted from gene amplification data. Instead, as discussed before, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation between gene amplification levels and protein levels. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants maintain, for the reasons provided in the previous response of January 9, 2006, that Pennica *et al.,* Hu *et al.* and Haynes *et al.* do not show that a lack of correlation between gene (DNA) amplification and elevated protein levels exists, in general, and further that references Orntoft *et al.*, Hyman *et al.* and Pollack *et al.* show that in general, there is a positive correlation between increased DNA levels and increased mRNA levels in the art.

Dr. Polakis states that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on his own factual findings.

The Examiner indicated that the Polakis Declaration was considered but provided no further comment.

Applicants further present a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA

and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions regarding protein data.

Both Polakis Declarations (Polakis I and II) are further supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (herein after Cell 3rd) and (4th ed. 2002) (excerpts attached as Exhibit 1). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that " [f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (Emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (Emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (copy enclosed under Exhibit 1) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (Emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (copy enclosed in Exhibit 1). Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." *Zhigang* at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002) (a copy enclosed in Exhibit 1) states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells…[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (Emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the Declarations of Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In addition to the supporting references previously submitted, Applicants submit herewith further references as additional support for their assertion that, changes in DNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

For example, in a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (copy enclosed as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix

metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA … and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. … There was a good correlation between expression of proteosome 20S alpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Misrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55

kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, *e.g.,* a decrease, lead to a corresponding change in the level of the encoded protein, *e.g.,* a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung or colon tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lung or colons. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lung or colons." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, *e.g.,* an increase, generally leads to a corresponding change in the level of protein expression, *e.g.,* an increase.

These studies are representative of <u>numerous</u> published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer support of Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast. Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in

DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good corr elation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases). " *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 148 references, in addition to the declarations and references already of record, to support Applicants' asserted utility. These references support the assertion that in general, a change in DNA levels for a particular gene leads to a corresponding change in the protein levels. As Applicants have previously acknowledged, the correlation between changes in DNA levels and protein levels is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in DNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

Therefore, Applicants request that the Examiner reconsider this rejection and maintain that they have demonstrated utility for the PRO1111 polypeptide. Applicants add that the gene amplification data clearly supports a role for PRO1111 as a lung or colon tumor marker. Accordingly, the present invention has utility for PRO1111 as a lung or colon tumor markers

under 35 U.S.C. §101 and Applicants should also be entitled to the earlier priority of at least **June 23, 1999**.

Claim Rejections – 35 U.S.C. 112, First Paragraph- Enablement

Claims 132-133 remain rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification "does not reasonably provide enablement for proteins that are encoded by a nucleic acid that is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon". Applicants submit that, for the same reasons discussed above, under the "priority" section, polypeptides having at least 95 to 99% amino acid sequence identity to the polypeptide of SEQ ID NO: 229 are enabled in this application. Moreover, as discussed in the response of January 9, 2006, Applicants claim only those variants which have both the recited sequence identity and biological function as described in the claims. Thus, these recitations clearly act to further define the claimed genus of Claims 132 and 133. One of skill in the art could readily make such variant polypeptide, since the specification clearly provides ample guidance on how to prepare PRO polypeptides with sequence identity, and further could also easily test such variants in the gene amplification assay, without any undue experimentation. Therefore, this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. 112, First Paragraph- Written Description

Claims 124, 126 and 130-133 are rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification "does not describe in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention".

Arguments

The Examiner rejected the claims based on references to the terms "extracellular domain" and "native sequences". Applicants have canceled references to these terms without prejudice or disclaimer, mainly to hasten prosecution in this case.

Further, pending Claims 132-133 were rejected, despite reciting the functional recitation that the nucleic acid encoding the claimed polypeptides are amplified in adenocarcinomas or squamous cell carcinomas of the lung, or in adenocarcinomas of the colon.

Current applicable case law holds that biological sequences are not adequately described solely by a description of their desired functional activities. It is, however, well established that a combination of functional and structural features suffices to describe a claimed genus, as discussed in the PTO's own Written Description Guidelines, and as set forth in *Enzo Biochem., Inc. v. Genprobe, Inc.* In *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard that "the written description requirement can be met by 'showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, . . . *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. While the invention in *Enzo* was still a DNA, the holding has been treated as being applicable to proteins as well. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids.

The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural recitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[1]

The instant claims recite structural features, namely, 95-99% sequence identity to the sequence of SEQ ID NO: 229. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acids are amplified in adenocarcinomas or squamous cell carcinomas of the lung, or in adenocarcinomas of the colon. The specification provides detailed guidance as to how to identify these recited variants of SEQ ID NO: 229, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence

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[1] M.P.E.P. §2163 II(A)(3)(a)

substitutions, as well as detailed protocols for determining whether a gene encoding a variant PRO1111 protein is amplified in particular tumor. Thus, one of skill in the art could easily identify whether a variant PRO1111 sequence falls within the parameters of the claimed invention. Further, the recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand. Accordingly, a description of the claimed genus has been achieved by the recitation of both structural and functional characteristics. Thus, the genus of polypeptides with at least 95-99% sequence identity to SEQ ID NO: 229, which possess the functional property of having a nucleic acid which are amplified in lung or colon tumors would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Accordingly, one skilled in the art would have known that Applicants had knowledge and possessed the claimed polypeptides with 95-99% sequence identity to SEQ ID NO: 229. As discussed above, a description of the claimed genus has been achieved and this rejections should be withdrawn.

Claim Rejections – 35 U.S.C. 112, Second Paragraph

Claims 132-133 are rejected under 35 U.S.C. §112, second paragraph, allegedly for reciting the term "native sequence polypeptide having at lease 95% sequence identity".

As discussed above, the term "native" has been removed from the instant claims, whereas the specification provides ample guidance for making and using polypeptides with 95-99% sequence identity to SEQ ID NO: 229.

Accordingly, the claims now meet the requirements of 35 U.S.C. §112, second paragraph and hence, this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §102- Prior art

As discussed under the priority section above, Applicants respectfully maintain that they are entitled to an effective filing date of at least **June 23, 1999** based on the 'gene amplification' assay results for PRO1111 polypeptides.

All rejections directed to canceled claim 127 are rendered moot.

1. Claims 124-127, 129 and 132-133 remain rejected under 35 U.S.C. §102(b) as being anticipated by Wang *et al.* (Genbank Accession No. AF196976; pub 10/20/1999).

2. Claims 124-127, 129 and 132-133, (Examiner mistakenly says 119-123 and 130-133) are rejected under 35 U.S.C. §102(a) or (b) as being anticipated by Jacobs *et al.* (WO 99/50405, pub date 10/7/99; or Genebank AAY28806, pub: October 7, 1999).

As discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims, and this date precedes the publication date for Wang *et al.* and Jacobs *et al.* Therefore, neither Wang nor Jacobs, nor Genbank Accession No. AAY28806 are prior art under 35 U.S.C. §102(a) or (b), and hence this rejection should be withdrawn.

3. Claims 124, 127 and 130-133 are rejected under 35 U.S.C. §102(e) as being anticipated by Shimkets et al. (U.S. Patent No. 6,689,866 dated 3/8/00).

Claims 119-123 have been canceled hence this rejection is moot for these claims. Further, as discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the currently pending claims. Shimkets is dated after the effective filing date of **June 23, 1999.** Therefore, Shimkets is not prior art and these rejections should be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

1) Claims 130 and 132-133 remain rejected under 35 U.S.C. §103(a) as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson *et al.*

2) Claim 131 is rejected under 35 U.S.C. §103(a) as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson *et al.* and further in view of U.S. Patent No. 5,116,964 (Capon).

Applicants respectfully remind the Examiner that the instant case is directed to **polypeptides**, particularly, to the polypeptide of SEQ ID NO:229, and not to nucleic acids. Applicants note that the polypeptide sequences encoded by AI769814, AI435407, AI470931 or T15752 were not reduced to practice in the cited art nor did the art provide any disclosure whatsoever of the full-length polypeptide encoded by any of these nucleic acid fragments. The Examiner says that utility under 101 is not required for finding obviousness and one skilled in the

art supposedly could make the DNAs disclose therein. However, these references had not taught one skilled in the art how to derive the rest of the DNA sequence, let alone, the instantly claimed polypeptide, at the time of filing. The USPTO acknowledges that EST sequences are not enabling and do not obviously teach full-length DNA sequences, or their encoding polypeptides Hence, this rejection for the instant polypeptide case based on nucleic acid ESTs alone is entirely inappropriate and AI769814, AI435407, AI470931 or T15752 cannot be viewed as prior art.

Since the primary references fall as prior art, and neither Sibson nor Capon teach SEQ ID NOs:229 nor 228 of the instant application, this rejection falls and should be withdrawn.

(3) Claim 131 is rejected under 35 U.S.C. §103(a) as being unpatentable over Wang *et al.* Genbank Accession No. AF196976; pub 10/20/1999, in view of U.S. Patent No. 5,116,964 (Capon).

For the reasons discussed above under section (2), and also because Applicants are at least entitled to an effective filing date of **June 23, 1999**, the primary reference Wang *et al.* is not prior art under 35 U.S.C. §102(a) or (b). Moreover, Capon does not teach SEQ ID NOs:229 nor 228 of the instant application, and thus, this rejection falls and should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No.**39780-2730 P1C17**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 29, 2006

Barrie Greene Reg. No. 46,740 for
Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000